# A response to Michael Lynch

MICHAEL J. BEHE[1] AND DAVID W. SNOKE[2]
[1]Department of Biological Sciences, Lehigh University, Bethlehem, Pennsylvania 18015, USA
[2]Department of Physics and Astronomy, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

We thank Michael Lynch for his interest in our work and *Protein Science* Editor-in-Chief Mark Hermodson for the opportunity to respond briefly to his Editorial and to Lynch's article.

It sometimes happens in science that there is a marked difference between the stories people tell about the implications of a work and the actual details of the work. Some people have made great hay about the implications of our article. We subscribe neither to triumphant views in some circles that our paper disproved Darwinism, nor to overwrought ones that it supports some grand anti-science conspiracy.

Our paper (Behe and Snoke 2004) contains one simple result. When reasonable parameters are used with our model to estimate actual time scales or population sizes for the evolution of multi-residue (MR) protein features, they are unrealistically large. This implies that the model we chose, which is restricted to point mutations and assumes intermediate states to be deleterious, isn't a plausible evolutionary pathway. One must therefore look about for a new model. We did not rule out such a possibility; in our original article, we explicitly stated, "we should look to more complicated pathways, perhaps involving insertion, deletion, recombination, selection of intermediate states, or other mechanisms, to account for most MR protein features."

In his Editorial (this issue), Professor Hermodson reports that comments sent to him assume a consensus, "Thus, intermediate states must also be assumed to be selected." Some significant previous work does not make this assumption (Kimura 1985; Ohta 1989), but our paper supports such a consensus. This is a strong requirement—that not only the end products, but steps along the way to a multi-residue function, must be either selected or at least neutral. Michael Lynch makes a similar assumption. Our model posited necessary intermediate mutations to be deleterious in the unduplicated gene; Lynch's model assumes them to be neutral: "all 20 amino acids are equally substitutable in the intermediate neutral state" (Lynch 2005, this issue). All of his objections to our work stem from this difference.

The following are specific comments regarding Lynch's article. All quoted material is either from his article (Lynch 2005, this issue) or ours (Behe and Snoke 2004).

1. Experimental studies contradict Lynch's assumption of complete neutrality as a rule; the majority of amino acid substitutions decrease protein function.
2. Lynch's and our models are not mutually exclusive. Some evolutionary pathways might involve both deleterious and neutral mutations.
3. Lynch writes in the section "The Model" that we "imply that all amino acid changes lead to nonfunctionalization." We imply no such thing. Although we assumed that intermediate mutations required for a new feature decreased function, we wrote, "it can be calculated that on average a given position will tolerate about six amino acid residues and still maintain function." Our estimation of $\rho$ explicitly takes into account the tolerance of sites for substitution.
4. In "The Model," Lynch writes, "As in Behe and Snoke (2004), this adaptation is assumed to be acquired at the expense of an essential function of the ancestral protein. . . ." We made no such assumption. In our model, the final mutation might restore and enhance the original function.
5. In the Discussion, Lynch writes, "It is difficult to pinpoint the source of the difference between the results of Behe and Snoke and those contained herein. . . ." The differences are largely due to opposing starting presumptions about whether mutations are deleterious.
6. In the Discussion, Lynch writes, "Behe and Snoke assume that the forward and backward point-mutation rates (per amino acid residue) are equal." We do not. The mutation rate we use is the nucleotide point-mutation rate.
7. In the Discussion, Lynch writes that we assume mutations have "lethal pleiotropic effects." We did

Reprint requests to: Dr. Michael J. Behe, Department of Biological Sciences, Lehigh University, 111 Research Drive, Bethlehem, PA 18015, USA; e-mail: mjb1@lehigh.edu; fax: (610) 758-4004.

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not assume mutations to be either lethal or pleiotropic. We only assumed that they are "strongly selected against."

8. In the Discussion, Lynch writes, "If the intermediate steps ... are entirely neutral after gene duplication, as Behe and Snoke assume, then there is no compelling reason that 'one-off' (type-2) alleles should be absent from the population prior to duplication." The reason for no "one-off" alleles before duplication in our model is that intermediate mutations are assumed to be deleterious in a single-copy gene.
9. In the Discussion, Lynch writes, "Behe and Snoke failed to realize that a completely linked pair of duplicate genes has a mutational advantage equal to the mutation rate to null alleles. ..." Such an effect does not hold for a model like ours in which intermediate mutations are postulated to be deleterious.
10. A recent report (Gao and Innan 2004) presents evidence that the gene duplication rate is lower by several orders of magnitude than that assumed both by Lynch and by us based on the work of Lynch and Conery (2000). If so, then both his and our calculations for the population sizes needed to fix a mutation in a duplicated gene are substantial underestimates.

We again thank Professor Lynch for his work in this important area.

## References

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